SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efudix® Cream 5%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Efudix contains 50 mg/g fluorouracil.

Excipients with known effect

Each gram of cream contains 150 mg of stearyl alcohol, 115 mg of propylene glycol, 50 mg of polysorbate 60, 0.25 mg of methyl parahydroxybenzoate and 0.15 mg of propyl parahydroxybenzoate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream

White, opaque cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antineoplastic agent to treat actinic keratosis multiple and superficial basal cell carcinoma.

4.2 Posology and method of administration

Efudix is for topical application.

Pre-malignant conditions

The cream should be applied thinly to the affected area once or twice daily; an occlusive dressing is not essential.

Malignant conditions

The cream should be applied once or twice daily under an occlusive dressing where this is practicable.

The cream should not harm healthy skin. Treatment should be continued until there is marked inflammatory response from the treated area, preferably with some erosion in the case of pre-malignant conditions.

Severe discomfort may be alleviated by the use of topical steroid cream. The usual duration of treatment for an initial course of therapy is three to four weeks, but this may be prolonged. Lesions on the face usually respond more quickly than those on the trunk or lower limbs whilst lesions on the hands and forearms respond more slowly. Healing may not be complete until one or two months after therapy is stopped.

Special population

Elderly

Many of the conditions for which fluorouracil is indicated are common in the elderly. No special precautions are necessary.

Paediatric population

In view of the lack of clinical data available, fluorouracil is not recommended for use in children.

4.3 Contraindications

Efudix is contraindicated in patients with known hypersensitivity to fluorouracil or any of the excipients listed in section 6.1. Coadministration of fluorouracil with antiviral nucleoside drugs (e.g., brivudine and analogues) may lead to a substantial increase in plasma levels of fluorouracil and associated toxicity and is contraindicated. Brivudine and analogues are potent inhibitors of DPD, a fluorouracil metabolising enzyme (see section 4.4 and 4.5).

Use of fluorouracil during pregnancy and in breast-feeding mothers is contraindicated.

4.4 Special warnings and precautions for use

The hands should be washed carefully after applying **Efudix**. Also care should be taken to avoid contact with mucous membranes or the eyes when applying the cream.

The total area of skin being treated with **Efudix** at any one time should not exceed 500 cm^2 (approximately 23 x 23 cm). Larger areas should be treated a section at a time.

The normal pattern of response includes: early and severe inflammatory phases (typically characterised by erythema, which may become intense and blotchy), a necrotic phase (characterised by skin erosion) and finally healing (when epithelialisation occurs). The clinical manifestation of response usually occurs in the second week of **Efudix** treatment. However, these treatment effects can sometimes be more severe and include pain, blistering and ulceration (see section 4.8). Occlusive dressing may increase inflammatory reactions of the skin. There is a possibility of increased absorption through ulcerated or inflamed skin (see section 5.2). Further application of **Efudix** should be avoided in cases of severe skin inflammation including ulceration and blistering.

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc.) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

Exposure to UV-radiation (e.g., natural sunlight, tanning salon) should be avoided.

Pre-existing subclinical lesions may become apparent following **Efudix** use.

Any severe skin discomfort during treatment with **Efudix** may be alleviated by the use of an appropriate topical steroid cream.

When used according to the approved prescribing information **Efudix** should have minimal effect on healthy skin.

Significant systemic drug toxicity is unlikely via percutaneous absorption of fluorouracil when **Efudix** is administered as per the approved prescribing information. However, the likelihood of this is increased if the product is used on skin areas in which the barrier function is impaired (e.g., cuts), if the product is applied under an occlusive dressing, and/or in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD). DPD is a key enzyme involved in metabolising and eliminating fluorouracil. Determination of DPD activity may be considered where systemic drug toxicity is confirmed or suspected. There have been reports of increased toxicity in patients who have reduced activity of the enzyme dihydropyrimidine dehydrogenase. In the event of suspected systemic drug toxicity, **Efudix** treatment should be stopped.

An interval of at least four weeks should elapse between treatment with brivudine, sorivudine or analogues and subsequent administration of **Efudix**.

The excipient stearyl alcohol may cause local skin reaction (e.g., contact dermatitis), the excipient propylene glycol may cause skin irritation, the excipients polysorbate 60, methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Although no significant drug interactions with fluorouracil have been reported, potential drug interactions are possible as indicated below.

Brivudine, sorivudine and analogues are potent inhibitors of DPD, a fluorouracil metabolising enzyme (see section 4.4). For this reason, concomitant administration of these drugs with **Efudix** is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Due to the genotoxic potential of fluorouracil, women of childbearing potential should use effective contraceptive measures while being treated with fluorouracil and for 6 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving fluorouracil and for 3 months following completion of treatment.

Pregnancy

There are no adequate data from the use of topical fluorouracil in pregnant women.

Studies in animals have shown that fluorouracil is teratogenic (see section 5.3). The potential risk for humans is unknown, hence **Efudix** should not be used during pregnancy (see section 4.3).

Women of childbearing potential should not become pregnant during topical fluorouracil therapy and should use effective method of contraception during treatment with fluorouracil therapy. If a pregnancy occurs during treatment the patient should be advised about the risk for the child of adverse effects associated with the treatment and genetic counselling is recommended.

Breast-feeding

No information is available on the excretion of fluorouracil into breast milk. Studies in animals have shown the fluorouracil is teratogenic (see section 5.3). A risk to the suckling child cannot be excluded, so **Efudix** should not be used in nursing mothers (see section 4.3). If use during breastfeeding is absolutely necessary, breastfeeding must be discontinued.

Fertility

No clinical data in humans is available on the effects of fluorouracil on fertility.

Experiments in various species revealed an impairment of the fertility and reproductive performance of systemic 5-fluorouracil. The reduced systemic exposure to 5-FU following its topical administration will reduce the potential toxicity. The use of topical 5-fluorouracil may impair female and male fertility. Topical fluorouracil is not recommended in men attempting to father a child.

4.7 Effects on ability to drive and use machines

It is unlikely that treatment will have any effect on the ability to drive and use machines when used according to the dosage instructions.

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000)
Frequency not known (cannot be estimated from the available data)

Adverse reactions associated with exacerbations of normal pattern of response (see section 4.4) which are related to pharmacological activity of fluorouracil on the skin are the most frequently reported reactions. Allergic type skin reactions and reactions related to systemic drug toxicity are very rarely reported.

Blood and lymphatic system disorders
Very rare: Haematological disorders, associated with systemic drug toxicity, e.g., pancytopenia, neutropenia, thrombocytopenia, leukocytosis.

Immune system disorders
Very rare: Allergic conditions (e.g., Hypersensitivity and Type IV hypersensitivity).

Nervous system disorders
Frequency not known: Dysgeusia, headache, dizziness.

Eye disorders
Frequency not known: Conjunctival irritation, keratitis, increased lacrimation.

Gastrointestinal disorders
Very rare: Diarrhoea haemorrhagic, diarrhoea, vomiting, abdominal pain, stomatitis, associated with systemic drug toxicity.
Frequency not known: Nausea.

Skin and subcutaneous tissue disorders
Very rare: Pruritus, urticaria, rash (usually local but also generalised if associated with systemic drug toxicity); erythemas including erythema multiforme; dermal and epidermal conditions (such as skin burning sensation, skin exfoliation, skin swelling); skin and subcutaneous skin ulcerations; dermatitis and eczema conditions (such as contact dermatitis, skin irritation); blisters, and alopecia.

Exposure to sunlight may increase the intensity of the reaction.

See also normal pattern of response in section 4.4.

General disorders and administration site conditions
Very rare: Pyrexia, chills and mucosal inflammation, associated with systemic drug toxicity.
Frequency not known: Application site haemorrhage.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

If **Efudix** is accidentally ingested, signs of fluorouracil overdosage may include nausea, vomiting and diarrhoea. Stomatitis and blood dyscrasias may occur in severe cases. Appropriate measures should be taken for the prevention of systemic infection and daily white cell counts should be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues, ATC code: L01BC02

Efudix is a topical cytostatic preparation which exerts a beneficial therapeutic effect on neoplastic and pre-neoplastic skin lesions while having less effect on normal cells. The pattern of response follows this sequence: erythema, vesiculation, erosion, ulceration, necrosis and epithelisation.

5.2 Pharmacokinetic properties

Fluorouracil is minimally systemically absorbed when applied topically to intact skin. When applied to the skin, the skin's barrier function is pathologically altered (e.g., as in ulceration), and the absorption rate can increase to 60%. In patients with AK, 2.4 – 6% of the topical dose was absorbed systemically. Similarly, under occlusion, significantly more fluorouracil is absorbed.
Fluorouracil may be metabolised by catabolic or anabolic routes which are similar to that of endogenous uracil.

5.3 Preclinical safety data

5-fluorouracil is genotoxic in mice and in vitro, embryotoxic and teratogenic in mice and rats, and is classified as possible human teratogen. Malformations occurred (defects in the nervous system, palate, skeleton, tails, limbs) in several species (including rat and Syrian golden hamsters). Embryotoxic effects (small fetus, resorption) are also observed in monkeys treated with 5-fluorouracil.

5-fluorouracil crosses the placenta.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
White soft paraffin
Stearyl alcohol
Propylene glycol
Polysorbate 60
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening the immediate packaging: 3 months.

6.4 Special precautions for storage
Storage
Store below 30 °C.

Dilution
Efudix should not be diluted.

6.5 Nature and contents of container
Efudix is supplied in a 20 g aluminium tube with a plastic screw cap.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Dexcel Ltd., 1 Dexcel St., Or Akiva 3060000, Israel.

8. MARKETING AUTHORISATION NUMBER
062-40-21478-00

Revised in August 2025 according to MOH guidelines.